Editorial Commentary

Lessons from STIMULI: who benefits from consolidation nivolumab and ipilimumab in limited-disease small-cell lung cancer after chemo-radiotherapy?

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Small-cell lung cancer (SCLC) is an aggressive malignancy that is characterized by early metastasis and poor prognosis. Only approximately 30% of all SCLC patients will present with limited disease (LD) at diagnosis. The preferred regimen of LD SCLC remains cisplatin or carboplatin plus etoposide applied with concurrent thoracic radiotherapy starting with the first or second chemotherapy cycle (1). Due to the absence of distant metastasis and the application of local therapy the intended therapeutic goal is long-term control and even cure of the disease. However, the aggressive character of the disease limits these expectations. Hence, despite treatment with curative intention applying concurrent chemoradiotherapy, the median survival is limited as are 5-year survival rates ranging from 25% to 33%. Consequently, strategies to improve cure are urgently needed. For example, consolidation therapy following concurrent chemoradiation therapy may improve overall survival but, in turn, may be challenged by toxicity. Moreover, question regarding the duration of consolidation therapy and patient selection would be needed to address.

Recently, in metastatic disease, the addition of anti-PD-L1 inhibitors such as atezolizumab or durvalumab to platinum and etoposide combinational chemotherapy has led to a significant increase of overall survival (hazard ratios of 0.76 and 0.71, respectively) (2-4). Moreover, the PACIFIC trial has demonstrated the curative character of consolidation checkpoint inhibitor therapy in stage III non-small cell lung cancer (NSCLC) by improving 5-year overall survival rate to 42.9% in patients treated with consolidation durvalumab therapy for one year compared to 33.4% in the control study arm (5). Consequently, these results have fostered interest whether the integration of checkpoint inhibitors would also lead to an improvement of survival in treatment strategies of LD extensive disease small cell lung cancer.

The phase II STIMULI trial randomized a total of 153 patients with LD SCLC to either consolidation immunotherapy versus observation after chemo-radiotherapy plus prophylactic cranial irradiation (PCI) (6). Consolidation immunotherapy consisted of four cycles of nivolumab plus ipilimumab every 3 weeks, followed by nivolumab monotherapy every 2 weeks for up to 12 months. The dosages used where similar to that of the CheckMate 032 study. In this phase I/II trial, 213 SCLC patients with disease with progressive disease after at least one platinum based chemotherapy regimen and a median or 2–3 prior treatment regimens were either assigned to nivolumab monotherapy or one of two different dosage regimens of nivolumab plus ipilimumab (7). The regimen of four cycles of 1 mg/kg nivolumab plus 3 mg/kg ipilimumab every 3 weeks followed by 3 mg/kg nivolumab every 2 weeks until disease progression or unacceptable toxicity led to a response rate of 21.9% and a median progression-free survival on 1.5 months (7).

The STIMULI study was designed, after a protocol amendment, to improve progression-free-survival (PFS) as the only primary endpoint. The aim of improving the hazard ratio of 0.57 should translate to a prolongation of PFS from 13.1 to 22.8 months. To achieve this aim, at

least 81 PFS events would be needed providing a power of 80%. As a comparison, the phase III PACIFIC study led to an improvement of PFS from randomization after definitive chemoradiation therapy with durvalumab consolidation therapy compared to placebo with a hazard ratio for disease progression or death of 0.52 in patients with stage III NSCLC (8). However, the STIMLU trial had to stop recruitment prematurely due to slow accrual after 153 patients had been randomized. Still, after 82 PFS events in the experimental arm, median PFS was similar between experimental and observation arms and a hazard ratio of 1.02. Of interest, in subgroup analyses, a higher benefit of nivolumab plus ipilimumab on overall survival and, to a weaker extent, on PFS was noted for patients having received a radiotherapy with a twice daily schedule; however, despite being pre-planned, these results are based on small patient numbers and should be interpreted with caution.

While the STIMULI trial was negative in regard of its primary endpoint, several questions may arise that I would like to address in the following: is there a benefit of a consolidation therapy with nivolumab plus ipilimumab in patients with limited SCLC disease after chemoradiation therapy? What is the risk—benefit ratio of such kind of a therapy? What is the benefit of adding an anti-CTLA antibody to a PD-1 checkpoint inhibitor? Would the efficacy be different if the checkpoint inhibitor treatment was added to the chemoradiation therapy? And, most certainly, could we preselect patients and how might we do it?

In addition to the lack of effect on PFS, with a median follow-up of 35.0 months, overall survival was not statistically different between both arms (hazard ratio of 0.95). However, the results of the phase II STIMULI should not be considered as definitive due to the limited power and patient number. The authors noted that one possible factor for the limited efficacy of the experimental arm could have been the short period on active treatment with a median of 1.7 months to discontinuation. Similar observations have been published in the three-arm, placebo-controlled, phase III Checkmate-451 trial where maintenance therapy with nivolumab plus ipilimumab did not prolong overall survival for patients with extensive disease (ED) SCLC (9). In the Checkmate-451 trial, only a median of 2.0 applications of maintenance ipilimumab plus nivolumab with the same dosages as used in the STIMULI trial could be delivered. One major factor leading to discontinuation was treatment-related toxicity which had been reported as 28.8% in patients treated with ipilimumab and nivolumab compared to 7.9% treated with nivolumab alone and 0.4% treated with placebo.

Interestingly, in the STIMULI trial, 55.1% of patients treated with the checkpoint inhibitor combination reported adverse events that lead to discontinuation. Moreover, checkpoint inhibitor treatment was associated with a risk of 51.3% in experiencing a treatment-related adverse event of grade 3 or higher. This risk is somewhat higher compared to the 29.9% of patients in the PACIFIC study where a grade 3 or 4 adverse event was reported after treatment with durvalumab monotherapy. Here, discontinuation due to adverse events leading to discontinuation occurred in 15.4% of patients in the durvalumab group and 9.8% in the placebo group. Likewise, pneumonitis as a particular interesting toxicity after chemoradiation treatment had been reported of grade 3 or 4 in 2.4% of patients who received durvalumab. In the STIMULI study, pneumonitis occurred in 28.2% for all grades and in 9% of grade 3 or higher in patients in the experimental arm. Toxicity was also a secondary endpoint in the Checkmate 032 trial where a combination of 1 mg/kg nivolumab plus 3 mg/kg ipilimumab seemed to be somewhat more toxic compared to 3 mg/kg nivolumab plus 1 mg/kg ipilimumab with more treatment-related grade 3 or 4 adverse events and a higher discontinuing rate because of toxicity despite a comparable clinical efficacy (7).

Even despite toxicity may have been affected by the previous radiochemotherapy treatment and cross trial comparison renders difficult, the toxicity of a combined checkpoint inhibitor treatment seems to be somewhat higher compared to single checkpoint inhibitor treatment. Certainly, physicians have learned to manage immunotherapy-related adverse events so even a higher risk for an immune-related toxicity could be discussed with the patient if there is an accompanied higher chance of clinical efficacy. Nevertheless, one may question the need of adding an anti-CTL4 antibody to checkpoint inhibitor therapy in SCLC in terms of efficacy.

Because anti-CTLA4 agents target different immune cell receptors and consequently alter regulation of distinct inhibitory pathways as compared to targeting the PD1 PD-L1 axis, there is a clear rationale why combinational checkpoint inhibitor therapy should be superior to monotherapy with anti-PD1 or anti-PD-L1 agents. However, several clinical studies failed to demonstrate increased efficacy. In the Checkmate 032 study, in pretreated ED SCLC patients, the combination of ipilimumab plus nivolumab led to an improved response rate (21.9% versus

11.6%) but similar overall survival as compared to nivolumab monotherapy (median 4.7 versus 5.7 months), respectively. In the Checkmate 451 trial, maintenance therapies consisting of neither ipilimumab plus nivolumab (hazard ratio of 0.92) nor nivolumab alone (hazard ratio of 0.84) were significantly superior to placebo treatment. Finally, in the CASPIAN study, the addition of tremelimumab to the combination of platinum, etoposide and durvalumab failed to improve overall survival or PFS (10).

Due to its study design, the STIMULI trial does not give a definitive answer to the question of the benefit of checkpoint inhibitors in LD SCLC and results cannot be considered definitive. Moreover, several trials are currently exploring the benefit of adding immunotherapy to standard therapy. A phase III trial with a similar design as STIMULI is evaluating a consolidation therapy of durvalumab plus tremelimumab, durvalumab monotherapy or placebo after concurrent chemoradiation therapy (NCT03703297). In addition, a phase II/III is testing the addition of atezolizumab to chemoradiation therapy with overall survival as the primary endpoint (NCT03811002). Of note, this latter trial combines the checkpoint inhibitor treatment already at the beginning of the chemoradiation therapy including the continuation of atezolizumab as consolidation therapy for up to one year. Similarly, several phase II trials explore chemoradiation therapy in combination with further anti-PD-1 or anti-PD-L1 antibodies such as sintilimab (NCT04189094) or durvalumab (NCT04602533). In addition, novel immune modulating targets are being evaluated. For example, a phase II trial is testing the combination of an anti-TIGIT antibody and an anti-PD-1 antibody to chemoradiation therapy (NCT04952597). Also, a phase III study is evaluating pembrolizumab combined with concurrent chemoradiation therapy followed by pembrolizumab plus the poly ADP-ribose polymerase (PARP) inhibitor olaparib for 12 months (NCT04624204). Primary outcome measures are PFS and overall survival.

However, in addition to exploring novel targets and novel combination strategies, we likely need novel patient selection criteria. Till date, there is no pre-selection factor that had hold promising clinical value in determining which patient is likely to benefit from the addition of checkpoint inhibitors. In contrast to studies on metastatic NSCLC, PD-L1 expression has not been predictive on the use of PD-L1 inhibitors in ED SCLC (2,3). Moreover, despite encouraging results in the Checkmate 032 study in posthoc analyses, extension of overall survival by checkpoint inhibitors was irrespective of tumor mutational burden in these studies (2,11,12). However, these analyses were exploratory and could only be performed on rather small subgroups compared to the intention-to-treat (ITT) population due to the lack of either tumor tissue or patient's blood. As a hypothesis, an inflamed gene signature has been proposed that may be distinguishing from other SCLC subgroups (13). Retrospectively, this classification of SCLC has been linked to chemotherapy or checkpoint inhibitor efficacy but warrants further research in a prospective way and consideration at the design of clinical studies. Possibly, different markers may be necessary depending on the intended modulation of immune system and the use of checkpoint inhibitor monotherapy or combination.

The development of anti-PD-1/PD-L1 or anti-CTLA4 modulating antibodies has established an entirely new field of anti-cancer therapy and significantly improved therapeutic efficacy in a variety of cancer entities. In SCLC, the addition of atezolizumab and durvalumab to platinum plus etoposide chemotherapy has set a new standard in treating ED SCLC. The STIMULI study has addressed the consequent question of adding checkpoint inhibitors to the treatment of LD SCLC. Despite failing to demonstrate improvement of PFS or overall survival, this question remains highly relevant and is being explored in further clinical trials. Nevertheless, there are several lessons to learn from STIMULI when developing this highly dynamic field further. Besides the question of the selection of the optimal targets, the identification of proper preselection factors would be extremely helpful. So far, for reasons outlined above, concurrent chemoradiation therapy remains the standard therapy in LD SCLC.

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